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(54) COMPOSITION FOR TREATMENT OF PRURITIS ANI

(71) We, BURTON PARSONS CHEMICALS INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, of 1515 "U" Street, N.W., Washington D.C., United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dermatological compositions for the treatment of fungal and bacterial infections, and more particularly to a combination of medicaments and carriers which can provide transepidermal penetration to the infection situs. Specifically, this invention provides a medicinal combination to combat pruritis ani without irritation or sensitization and without the use of antibiotics.

Infections caused by bacteria, fungi or yeast are generally successfully treated by standard chemical or antibiotic therapy. However, some infections cannot be satisfactorily treated by such means because of their situs and degree. This is particularly true in the case of pruritis ani. The peri-anal region is especially susceptible to infective development because the skin folds encourage retention of faecal matter which provides an ideal environment for the growth of parasitic organisms. The causes of such ailment include poor anal hygiene, irritating soaps, allergic conditions and local rectal diseases, which allow infectious and parasitic agents to penetrate the outer skin layers.

Pruritis ani may be quite mild with satisfactory treatment being a soothing salve to alleviate the itch. However, it also can be quite severe, and in some cases hospitalization is necessary before a cure is effected. Local therapy consists primarily of sitz-baths with potassium permangenate and compresses impregnated with silver nitrate. Castellani's paste or zinc undecylenate are also prescribed. Where there is considerable lichenfication, a specific anti-pruritic lotion is generally used, while more recently resort has been made to cortisone and antibiotics. As a final drastic alternative, X-ray treatment or surgical techniques may successfully alleviate the pruritis.

Even after these techniques have successfully eliminated all factors of etiology, the pruritis continues because of the skin change induced during the treatment. This latter condition is oftentimes induced by the medication applied in that one of the major problems of prurities ani is to bring the active medicament into direct contact with the causative organism, particularly when the latter is of fungal nature. Generally, sclerosing agents are combined with the medicament, the former ridding the infected anal area of dead cells and debris, whereby the top layer of skin is pulled away and the medicament allowed to penetrate deeply. This technique obviously leaves the treated region, although free of fungal infection, in a highly sensitized and painful state. Also, such treatment may leave the treated area in a dry condition, with resulting skin scaling.

Most medicaments for the treatment of pruritis ani contain at least some ingredient which will stain and discolour any clothing which might contact the treated area. Since air presence is desirable and the area being treated is quite difficult to bandage, many patients fail to complete the treatment, once the most severe symptoms of the pruritis have diminished.

The present invention is based on the recognition that N-trichloromethylmercapto-4 - cyclohexene - 1,2 - dicarboximide has excellent bactericidal and fungicidal properties, being effective against both gram negative and positive bacteria, fungi and yeast, when applied to pruritis affected areas, but is extremely difficult to apply to such areas. Although N - trichloromethylmercapto - 4 -

[Price 5s. 0d. (25p)]

cyclohexene - 1,2 - dicarboximide is a stable dry powder and may be incorporated into some emulsions, it is not stable in water. It may be carried by some conventional carriers such as polyethylene or polypropylene glycols, but is insufficiently soluble therein, so in such media it will not penetrate to the infection situs. It is both soluble and stable in alcoholic or other hydrocarbon media, but the use thereof is not possible in treatment of pruritis ani because of the application area. Noting that substantially all conventional carriers such as described above are either harmful to the skin or fail to provide stable carrier properties with full transepidermal penetration, it has been discovered that the dicarboximide may be stabilized and carried to an infected situs by combining it with polyvinylpyrrolidone in hexamethyl tetracosane (hydrogenated squalene). The polyvinylpyrrolidone acts as a stabilizer for the dicarboximide compound while being non-harmful to the skin. The hydrogenated squalene carries the combination to and through the skin layers without adversely affecting the stability of the polyvinylpyrrolidone - dicarboximide blend. Furthermore, this material itself dissolves lipoprotein, mixes fully with sebum, decreases water loss, stimulates skin respiration and aids in transfolicular and transepidermal penetration of not only the dicarboximide-polyvinyl-pyrrolidone blend, but also additional desirable medicaments as will be discussed later in this specification.

According to the present invention there is provided a composition for the treatment of pruritis ani consisting essentially of N - trichloromethylmercapto - 4 - cyclohexene - 1,2 - dicarboximide as an active fungicide and bactericide, polyvinylpyrrolidone as a stabilizer for the dicarboximide, and hydrogenated squalene as an active carrier for transepidermal penetration of the composition.

The combination of the three above noted components is generally blended with conventional emoluments to vary the composition strength. Additionally, other specific or general purpose medicaments may be combined in the composition for their known effects.

In order to provide the most effective action, in a composition including an ointment base the dicarboximide should be present in amounts of from .1 to 2% by weight, based on the overall composition, most advantageous results being obtained with about .8% by weight. The polyvinylpyrrolidone carrier amount is generally based on the amount of N - trichloromethyl - mercapto - 4 - cyclohexene - 1,2 - dicarboximide with the amount of the former being about 3 1/2 times the amount of the latter on a weight basis. Preferably, it forms from 0.3 to 6% by weight of the composition. To complete the critical combination, from 5 to 10% by weight of hydrogenated squalene is used, maximum transepidermal penetration of the medicament being obtained with about 7½ weight percent, based on the weight of composition.

As other desirable components for a most effective composition, the following are included:

diperodonmonohydrate:
allantoin;
oxycholesterin or other cholesterol derivatives;
hydrocortisone; and
a di, tri or tetra sodium salt of ethylenediaminetetraacetic acid.

As an ointment base a blend of polyethyleneglycols with cetyl alcohol is most suitable as the ointment is then water-washable. This base may also include N-methyl-2-pyrrolidone which may supplement or partially replace the above blend and which aids in solubilizing the dicarboximide. When so used, the N - methyl - 2 - pyrrolidone generally is present in amounts up to 6 cc per gram of dicarboximide, such amount being sufficient for solution and to improve the spreadability of the composition.

The diperodonmonohydrate provides local anaesthetic properties and may be utilized in amounts from 1 to 3%. Alternative local anaesthetics may be substituted or used in combination therewith, such as tetracaine, or benzocaine.

Allantoin or salts thereof (see e.g. U.S. 3,107,252) is a well known component in skin treatment compositions. For the composition of the invention, it has been found to possess both bacteriostatic and fungicidal properties while acting to accelerate cellular growth for fast healing. Its use in amounts of from 1 to 3% by weight appears to produce maximum desired effects.

Oxycholesterin is a natural constituent of the skin representing about 4% of the normal seba. It aids in replenishing the cells and thereby accelerates normal skin growth. Alternative materials for this component include other known cell replenishers, such as lanolin or its derivatives, cholesterol stearate or palmitate and certain aliphatic alcohols. These components are preferably used in amounts of from .5 to 3% by weight for substantial skin replenishment.

The use of hydrocortisone in the composition in amounts up to 2% by weight acts to soothe and heal the infected area and provide anti-inflammatory action after the pruritis is substantially alleviated.

A sequestering agent, such as ethylenediaminetetraacetate (di, tri, tetra - sodium) completes the preferred formulation, acting in amounts of up to .5% by weight to sequester trace metals from the infected site and to control pH to that of normal skin.

Citric acid may be substituted for the ethylenediaminetetraacetate.

Having generally described both the broad and preferred metes and bounds of the invention, the following is an example of a preferred formulation thereof.

EXAMPLE

The following ointment blend was prepared under sterile conditions:

Active Components	% (by weight)	Amt (grams)
N-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide (Vancide — R. T. Vanderbilt & Co. Inc.)	.8	20.00
Polyvinylpyrrolidone (Plasdone C — General Aniline & Film Corp.)	2.8	70.00
Hydrogenated squalene (Robane — Robeco Chemical, Inc.	7.6	190.00
Allantoin (National Polychemicals, Inc.)	1.4	35.00
Diperodon monohydrate (S.B.. Penick & Co.)	.1	5.00
Oxycholesterin (Falba — Pfaltz & Bauer, Inc.)	1.4	35.00
Ethylenediaminetetraacetic acid disodium salt (Lamont Laboratories)	.1	2.50
Ointment Base		Amt (grams)
Polyethylene glycol (Carbowax 4000)		650.00
Polyethylene glycol (Carbowax 400)		1370.50
Cetyl alcohol		72.00
		2500.00

(Carbowax is a Registered Trade Mark)

The above formulation was supplied to 27 reporting patients suffering from severe pruritis ani. Each patient was instructed to use the preparation by infection situs application twice a day for two weeks, after which both subjective and clinical appraisal were to be reported. The results of this study were as follows:

1. Sixteen patients reported excellent results, with complete disappearance of all symptoms. The patients reported no remaining discomfort and clinical examinations showed substantially complete healing and normal skin development.

2. Seven patients reported good to fair results, with substantial symptoms alleviation and partial healing. Clinical studies confirmed the patients' report, showing substantial diminution of the infection area.

3. Four patients reported no substantial condition improvement, but failed to show up for clinical evaluation.

4. In no case, either reported or clinically evaluated, was there any evidence of symptom aggravation.

The ointments of the invention may be provided with standard colouring agents or excipients such as perfume, the only requirement for such additives being that they be non-irritating to the skin or reactive with the ointment components. Since none of the basic components of the invention are antibiotics, the costs of compounding the formulation are substantially less than those in which antibiotics are utilized.

Although this specification has described the application of the composition to the peri-anal region, it is to be noted that the composition may be applied to any external infected situs even where sensitivity and penetration are not severe problems.

WHAT WE CLAIM IS:—

1. A composition for the treatment of pruritis ani consisting essentially of N-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide as an active fungicide and bactericide, polyvinylpyrrolidone as a stabilizer for the dicarboximide, and hydrogenated squalene as an active carrier for transepidermal penetration of the composition.

2. A composition according to Claim 1, including an ointment base wherein the dicarboximide is present in amounts of from 0.1 to 2% by weight; the polyvinylpyrrolidone from 0.3 to 6% by weight and the hydrogenated squalene from 5 to 10% by weight.

3. A composition according to Claim 2, wherein the ointment base consists essentially of polyethylene glycols and cetyl alcohol.

4. A composition according to Claim 2 or 3, wherein the ointment base includes N-methyl-2-pyrrolidone.

5. A composition according to any of Claims 2 to 4 including from 1 to 3% by weight allantoin.

6. A composition according to any of Claims 2 to 5 including from 0.5 to 3% by weight oxycholesterin.

7. A composition according to any of Claims 2 to 6 including up to 2% by weight hydrocortisone.

8. A composition according to any of Claims 2 to 7 including up to 0.5% by weight of a sequestering agent.

9. A composition according to Claim 8, wherein the sequestering agent is a di-, tri- or tetra-sodium salt of ethylenediaminetetraacetic acid.

10. A composition according to any one of Claims 2 to 9, which also contains from 1 to 3% by weight of a local anaesthetic selected from diperodon monohydrate, tetracaine and benzocaine.

11. A composition according to Claim 1 substantially as hereinbefore described.

12. A composition according to Claim 1 substantially as shown in the Example.

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